1
General Principles

Aims

The aims of the first chapter of this book are to provide the foundations for functional group chemistry. By the end of this chapter you should be able to understand:

- The relationship between bonding and structure of organic compounds
- The oxidative and substitutive relationship between functional groups
- The relationship between electronegativity differences and the reactivity of functional groups
- The reactivity of nucleophilic, electrophilic and radical reagents
- The role of acids and bases in the catalysis of organic reactions
- The influence of electronic and steric factors on reactivity
- The kinetic and thermodynamic control of reaction products

1.1 The Structure of Functional Groups

A functional group is a chemically reactive group of atoms within a molecule. Each functional group has its characteristic reactivity, which may be modified by its position within the molecule or by the presence of other neighbouring functional groups.

1.1.1 Hybridization and Bonding

An isolated carbon atom possesses two electrons in its 1s orbital, two electrons in its 2s orbital and two electrons in its 2p orbitals. The types of bonding found in carbon compounds arise from various hybrids of the 2s and 2p orbitals. Combination of one 2s and three 2p orbitals

1.1   **1.2**

1.3

1.4

1.5

$$H-C{\equiv}C-H$$

1.6
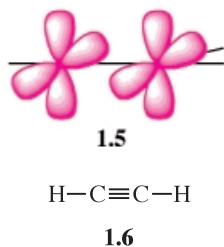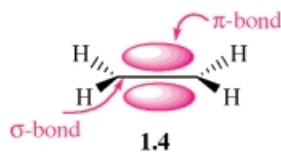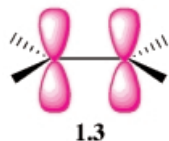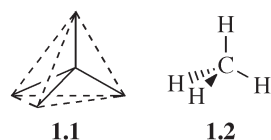
leads to four equivalent **sp³ hybridized** orbitals directed towards the apices of a tetrahedron (see **1.1**). Each of these orbitals can be occupied by one of the four available electrons from the carbon atom. These can each pair with one electron from another atom to produce, for example, methane (**1.2**). The energy required for the reorganization of the orbitals is gained from the formation of the four covalent bonds.

Alternatively, the 2s and two 2p orbitals may be hybridized to give a planar **sp²** system accommodating three electrons from the carbon, one in each hybrid orbital. Three bonds may then be formed with other atoms (see **1.3**). The remaining electron, which is in a p orbital at 90° to the plane of the sp² system, may overlap with a comparable p orbital from a second atom to form a **π-bond**, leading to a double bond between the carbon and this atom as in ethene (**1.4**).

A further way of making four bonds from the carbon is to hybridize the 2s and one 2p orbital to give two **sp** hybrids in which the orbitals are at 180° to each other. The remaining two 2p orbitals are used to form two π-bonds at 90° each other (see **1.5**). In this case there is a triple bond between the carbon and another atom as, for example, in ethyne (acetylene, **1.6**).

These hybridizations have several consequences. Since an s orbital is closer to the nucleus than the corresponding p orbital, the increasing s character in the orbitals in changing from sp³ to sp² and then sp leads to a decrease in bond length: sp³ C–C, 0.154 nm; sp² C=C, 0.134 nm; sp C≡C, 0.120 nm. Secondly, the increasing s character means that the bonding electrons in the sp and sp² orbitals are held more tightly to the carbon than in an sp³ bond. This is reflected in the increase in the polarity and acidity of a C^--H^+ bond and in the ease of formation of organometallic compounds containing the C^--M^+ bond. These follow the order sp³ < sp² < sp. On the other hand, there is an increase in the difficulty of breaking a carbon–halogen bond in the ionic sense C^+-X^-, in changing from an alkyl to an alkenyl (vinyl) halide. Thirdly, whereas the maximum electron density of a σ-bond lies between the atoms forming the bond, that of a π-bond lies above and below the plane of the bonding atoms, *i.e.* a π-bond is more exposed for reaction.

A further consequence lies in the opportunity for one π-bond to interact with another suitably oriented π-bond to give a **conjugated** system. When a carbon–carbon double bond is separated from another carbon multiple bond by one carbon–carbon single bond so that overlap is possible between the π-bonds, they are said to be conjugated. Thus in butadiene (**1.7**) molecular orbitals may be written embracing all four atoms. These conjugated double bonds often behave as one functional group rather than as two isolated double bonds. Electronic effects are relayed through the conjugated system.
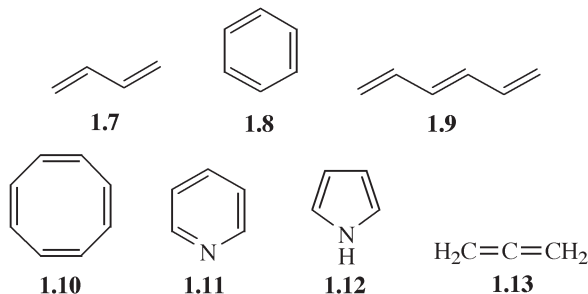
A cyclic conjugated system containing $(4n + 2)\pi$ electrons has an extra stability over that of a comparable number of isolated double bonds. This extra stabilization, known as **aromaticity**, leads to a characteristic pattern of reactivity which distinguishes the reactions of benzene (**1.8**) from, for example, the linear hexatriene (**1.9**) or cyclooctatetraene (**1.10**) ($4n$ electrons, $n = 2$). The aromatic sextet may arise not just from the overlap of three double bonds as in benzene (**1.8**) or pyridine (**1.11**) but also from the participation of the lone pair of electrons on a heteroatom. Thus pyrrole (**1.12**), with effectively six π-electrons, shows some aromatic character. In allene (**1.13**) the double bonds are at 90° to each other and conjugation does not occur.

1.1.2 Bonding and Structure

The tetrahedral arrangement of the bonds of an sp^3 hybridized carbon atom, the planar trigonal sp^2 arrangement and the linear sp system each have structural and geometrical consequences. The existence of free rotation about a single bond means that in a molecule such as ethane the methyl groups are free to take up a range of different **conformations** relative to each other. There are two extreme conformations, one in which the hydrogen atoms are staggered (see **1.14**) and the other in which they are eclipsed (see **1.15**). In the former the interactions between the hydrogen atoms of the methyl group are minimized, and the structure is of a lower energy than that in which the hydrogen atoms are eclipsed.
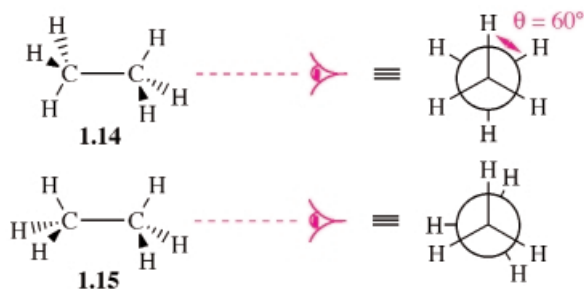
When these ideas are extended to butane, there are three **rotamers** about the central C–C bond which need to be considered. Not only are there the extremes of the staggered (**1.16**) and eclipsed conformations (**1.17**), in which the methyl group interactions are at a minimum and a maximum respectively, but there is also a *gauche* conformation (**1.18**) which is intermediate between these.

1.16   **1.17**   **1.18**

1.19 boat   **1.20** chair

1.21

1.22
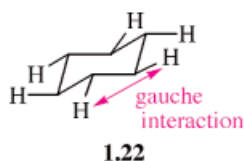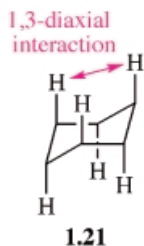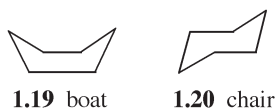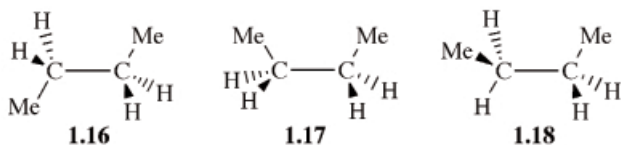
When the carbon chain is constrained in a cyclohexane ring, there are two extreme conformations known as the **boat** (**1.19**) and **chair** (**1.20**) forms. The former is destabilized by eclipsed interactions whilst in the latter the interactions are *gauche*. This conformation is more stable.
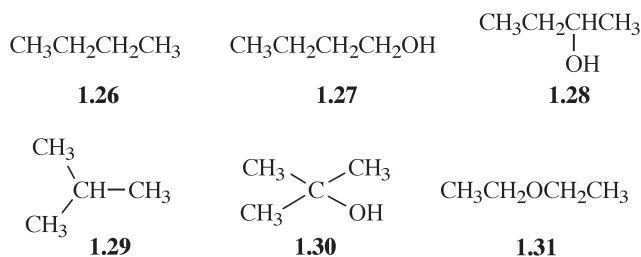
The C–H bonds on the chair cyclohexane ring are of two types. One set of six C–H bonds are parallel to the axis of the ring and are known as **axial** bonds (see **1.21**). The other set of six bonds point out of the horizontal plane of the ring and are known as the **equatorial** bonds (see **1.22**). When these C–H bonds are replaced by substituents, the substituents experience different interactions depending on their conformation. These steric relationships play an important role in the influence of the carbon skeleton of a particular compound on the reactivity of its functional groups.

In an alkene such as ethene, the presence of the π-bond prevents rotation about the C=C bond. The hydrogen atoms on the separate carbons are either *cis* or *trans* to each other. When the alkene bears substituents on the separate carbon atoms, these are *cis* or *trans* to each other. Distinct **geometric isomers** are possible. These compounds have different properties. Thus *cis*-ethenedicarboxylic acid is maleic acid (**1.23**). The carboxyl groups are close together in space and react together to form a cyclic anhydride (**1.24**). On the other hand, *trans*-ethenedicarboxylic acid is fumaric acid (**1.25**) and no such interaction is possible.

1.23   **1.24**   **1.25**
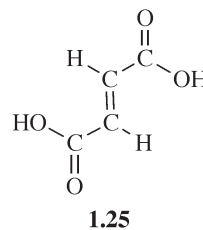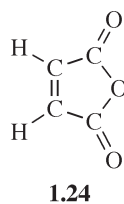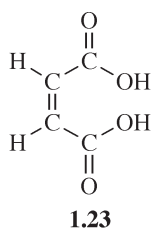
1.1.3 The Inter-relationship of Functional Groups

Functional groups may be regarded in a systematic, formal sense to be related by a series of redox and substitutive transformations. Replacement of a hydrogen atom on the carbon atom at the end of the four-carbon chain of butane (**1.26**) by a **hydroxyl** (OH) group gives the **primary alcohol** butan-1-ol (**1.27**), and when one of the methylene (CH$_2$) hydrogen atoms of butane (**1.26**) is replaced we obtain the **secondary alcohol** butan-2-ol (**1.28**). Replacement of the central hydrogen of the C$_4$ isomer 2-methylpropane (**1.29**) by an OH group gives 2-methylpropan-2-ol (**1.30**), a **tertiary alcohol**. In each of these isomeric alcohols there is a hydroxyl (OH) group conferring similar properties. However, the alcohols differ in the number of hydrogen atoms attached to the carbon atom and hence in the properties associated with these atoms. Insertion of the oxygen between the two central carbon atoms gives a further C$_4$H$_{10}$O isomer, ethoxyethane (diethyl ether, **1.31**), lacking the characteristic OH of the alcohol and thus containing a different functional group, the **ether** group.
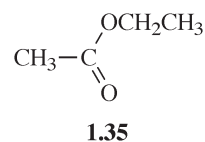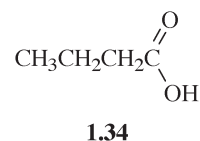
$$CH_3CH_2CH_2CH_3 \qquad CH_3CH_2CH_2CH_2OH \qquad \begin{matrix} CH_3CH_2CHCH_3 \\ | \\ OH \end{matrix}$$

$$\textbf{1.26} \qquad\qquad\qquad \textbf{1.27} \qquad\qquad\qquad \textbf{1.28}$$
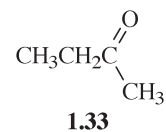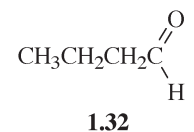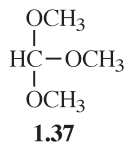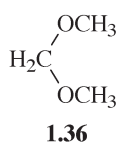
1.29

1.30

$$CH_3CH_2OCH_2CH_3$$

1.31

Oxidation of butan-1-ol gives butanal (**1.32**) which is characterized by a C=O, a **carbonyl** group, in this case an **aldehyde** group. Oxidation of the secondary alcohol butan-2-ol (**1.28**) gives butan-2-one (**1.33**), a **ketone**. There are many common properties of aldehydes and ketones, and others that differ because of the aldehydic C–H.

Oxidation of butanal leads to a **carboxylic acid**, butanoic acid (**1.34**). The distinctive properties of a carboxylic acid [C(=O)OH] can be considered as combining those of a carbonyl group modified by an attached hydroxyl group and those of a hydroxyl group modified by an attached carbonyl group. Replacement of the hydrogen atom of a carboxylic acid by an alkyl group gives an ester, for example ethyl acetate (ethyl ethanoate, **1.35**).

The functional group which contains two alkoxy groups attached to the same carbon atom occurs, for example, in dimethoxymethane (**1.36**), and is known as an **acetal**. A compound containing three alkoxy groups (see **1.37**) is an **ortho ester**.

If another atom such as a halogen, a sulfur or a nitrogen is substi-

1.32

1.33

1.34

1.35

$$H_2C \overset{OCH_3}{\underset{OCH_3}{<}}$$

1.36

$$HC \overset{OCH_3}{\underset{OCH_3}{\mid}} OCH_3$$

1.37

tuted in place of the hydroxyl group, further functional groups are generated (see Box 1.1).

**Box 1.1 Functional Groups Derived from Alcohols and Carboxylic Acids by Substitution**

| R–OH	alcohol	RC(=O)–OH	carboxylic acid
R–Cl	alkyl chloride (alkyl halide)	RC(=O)–Cl	acyl chloride
R–SH	thiol (sulfane)	RC(=O)–SH	thioacid
R–NH$_2$	amine	RC(=O)–NH$_2$	amide

where R is an alkyl group.

The **alkyl halides** (halogenoalkanes), **thiols** and **amines** are at the same oxidation level as the alcohols, while **acyl halides**, **thioacids** and **amides** are similarly related to the carboxylic acids. Like oxygen, sulfur can be inserted into a chain to generate the equivalent of an ether such as the **thioether**.

The tervalency of nitrogen does not permit simple insertion; another group such as hydrogen or an alkyl group must be added to nitrogen, producing for example $(CH_3)_2NH$ (dimethylamine, a **secondary amine**) or $(CH_3)_3N$ (trimethylamine, a **tertiary amine**). Note that the terms primary, secondary and tertiary are used in different ways when referring to alcohols and amines.

Tertiary amines can form stable **quaternary ammonium salts** ($R_4N^+X^-$), while thioethers form **sulfonium salts** ($R_3S^+X^-$), but stable **oxonium salts** ($R_3O^+X^-$) are less common.

$$CH_3CH_3 \longrightarrow CH_2{=}CH_2 \longleftarrow CH_3CH_2OH$$

1.38   **1.39**   **1.40**
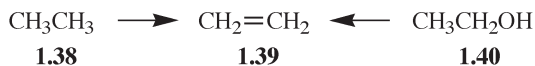
Dehydrogenation of alkanes such as ethane (**1.38**) relates them to **alkenes** such as ethene (ethylene, **1.39**). The same functional group may be obtained by dehydration of ethanol (**1.40**). Further dehydrogenation of ethene would generate an **alkyne**, ethyne (acetylene, **1.41**). In terms of oxidation level, the alkene is related to the alcohol and the alkyne is related to the ketone.

$$H{-}C{\equiv}C{-}H$$

1.41
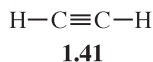
1.1.4 Electronegativity

Having considered the oxidative and substitutive relationships between functional groups, we now consider the factors that contribute to their

reactivity. The **electronegativity** of an element is a measure of the power of an element to attract electrons to itself in a chemical bond. It increases across a period in the Periodic Table from lithium to fluorine and decreases down a group. Electronegativity differences between atoms lead to an unequal sharing of the bonding electrons between the atoms concerned and consequently to regions of electron deficiency and electron excess in a molecule. Some electronegativities on the Pauling scale (lithium = 1 and fluorine = 4) are given in Table 1.1.

Table 1.1 Some Pauling electronegativity values

|						
H 2.1						
Li 1.0	Mg 1.2	B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
			Si 1.8	P 2.1	S 2.5	Cl 3.0
			Ge 1.8	As 2.0	Se 2.4	Br 2.8
						I 2.5

The halogens, oxygen and nitrogen are more electronegative than carbon and hence the alkyl halides, carbonyl and imine groups may be represented as in **1.42**–**1.44**, where the full-headed arrows represent the shift of an electron pair.

However, this is not a complete picture of the factors that contribute to the reactivity of functional groups. For example, the electronegativity difference between carbon and iodine is relatively small. In the much larger iodine atom the bonding orbitals are further from the nucleus than in chlorine and are more polarizable during the course of a reaction. These differences affect both the σ- and π-bonds. Thus many of the reactions of the alkyl halides and of carbonyl compounds may be rationalized in terms of the **polarization** of the bonds and the **polarizability** of the component atoms.
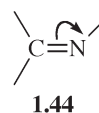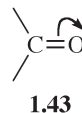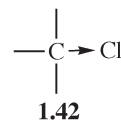
1.1.5 The Role of Lone Pairs

The non-bonding 'lone pairs' of electrons, particularly on oxygen and nitrogen, are far from inert and play an important role in directing the outcome of many reactions. They may accept a proton or a Lewis acid and thus increase the electron deficiency of the carbon atom to which they are attached. Secondly, they are available for donation to an attached electron-deficient carbon, and thus they may reduce the sensitivity of this carbon to nucleophilic attack. Thirdly, they are available for conjugation with the π-electrons of an alkene or arene, thus increasing its electron-rich character. These effects may be summarized in **1.45**–**1.47**. When two oxygen atoms, each possessing lone pairs, are

1.42

1.43   **1.44**

1.45

1.46   **1.47**
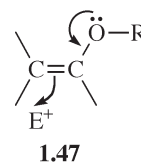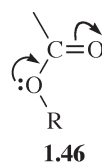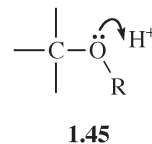
attached to the same carbon atom, the interactions between the lone pairs become important in determining the stereochemistry of reactions.

1.1.6 Resonance

1.48   **1.49**
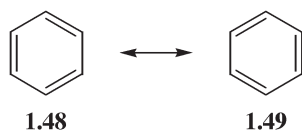
The structures of a number of compounds that contain a conjugated π-system can be written as the combination of a number of contributory valence bond structures. Thus benzene can be written as a combination of the two valence bond structures **1.48** and **1.49**. These contributory but non-isolable structures are known as resonance structures. The delocalization of the π-electrons, arising from the combination of these valence bond structures, leads to enhanced stability.
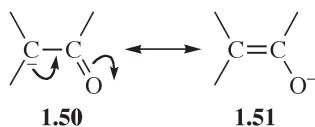
Examination of the contributory resonance structures can shed a useful light on the regions of electron deficiency and electron excess in a molecule and hence on its reactivity. The delocalization of charge through a conjugated system can give significant stabilization to reaction intermediates. An example is the delocalization of the negative charge of a carbanion adjacent to a carbonyl group (see **1.50** and **1.51**).

1.50   **1.51**

There are a number of rules that distinguish meaningful contributory resonance structures. Firstly, the atoms involved must not move between resonance structures; secondly, the same number of paired electrons should exist in each structure contributing to the resonance hybrid; and thirdly, structures that have adjacent like charges will not make a major contribution to the overall resonance hybrid, neither will those involving multiple isolated charges. Finally, it is important that the σ-bond framework, and in particular steric factors, permit a planar relationship between the contributory resonance structures.

1.1.7 Tautomerism

Compounds whose structures differ in the arrangement of hydrogen atoms and which are in rapid equilibrium are called tautomers. It is important to draw a distinction between resonance forms and tautomers. Whereas it is possible to obtain spectroscopic information on the existence of the individual tautomeric forms, resonance forms are not distinguishable. The difference can be illustrated by considering an amide (**1.52**). The resonance form (**1.53**) shows a difference in the position of charge, while the tautomer (**1.54**) shows a difference in the position of a hydrogen atom.

1.52   resonance   **1.53**   tautomerism   **1.54**
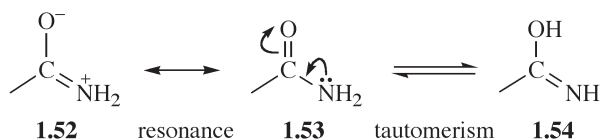
A number of common tautomeric relationships are shown in Box 1.2.

Box 1.2 Tautomeric Relationships
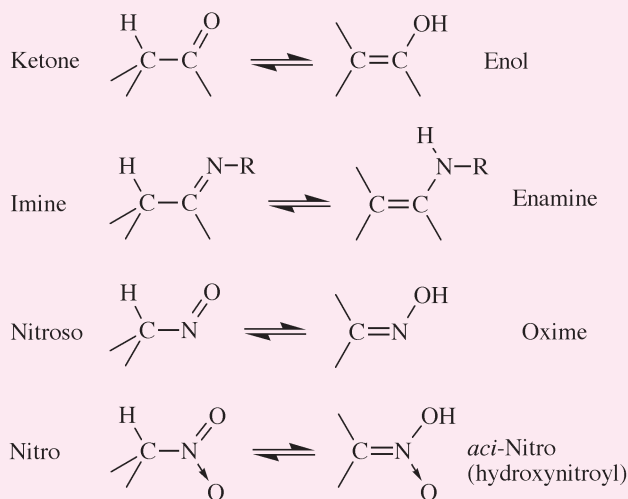
1.1.8 Naming of Compounds

Many simple common compounds are known by both a *trivial* and a *systematic* name. The systematic names are helpful in learning the structures of organic compounds, but the trivial names are often simpler and can reflect the source or dominant reactivity of the compound concerned. The systematic name for a compound has a *stem* that describes the carbon skeleton, *prefixes* and *suffixes* that indicate the functional groups, and *numbers* (locants) that define their position. Prefixes may also be added to indicate modifications to the carbon skeleton and to define the stereochemistry. A list of the more common prefixes, suffixes and stems is given in Table 1.2.

Thus the various $C_4H_{10}O$ alcohols are named as butan-1-ol [$CH_3CH_2CH_2CH_2OH$], butan-2-ol [$CH_3CH_2CH(OH)CH_3$], 2-methyl-propan-1-ol [$(CH_3)_2CHCH_2OH$] and 2-methylpropan-2-ol [$(CH_3)_3COH$]. In selecting a stem, note that this includes the carbon atom of the substituent described by the suffix. For example, ethanoic acid (acetic acid) is CH_3CO_2H, not $CH_3CH_2CO_2H$ (propanoic acid). Where there is chain branching, the longest chain is selected as the stem. For example, $CH_3CH_2CH(CH_3)CH_2OH$ is named as 2-methylbutan-1-ol and not as 2-ethylpropan-1-ol.

The relative positions of substituents on an aromatic ring (*e.g.* benzene) are indicated by numbers (see **1.55**). When only two substituents
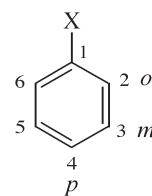
1.55

Table 1.2 Common stems, suffixes and prefixes

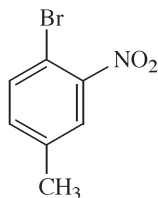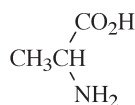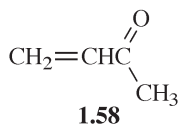*Examples of stems for carbon chain length*

C_1	meth-	C_4	but(a)-	C_7	hept(a)-	C_{10}	dec(a)-
C_2	eth-	C_5	pent(a)-	C_8	oct(a)-		
C_3	prop(a)-	C_6	hex(a)-	C_9	non(a)-		

Examples of suffixes

-ane	alkane	-oic acid	carboxylic acid
-ene	alkene	-oate	ester or salt
-yne	alkyne	-oyl	acyl derivative
-ol	alcohol	-yl	alkyl derivative
-al	aldehyde	-amine	amine
-one	ketone	-di-, -tri-	two or three of

Examples of prefixes

cyclo-	amino-	hydroxy-
cis/trans-	bromo-	iodo-
(±)-	chloro-	methyl-
	fluoro-	nitro-

are present, *o-* (*ortho*), *m-* (*meta*) and *p-* (*para*) are sometimes used in place of 1,2-, 1,3- and 1,4-, respectively. These may also be used to relate two particular substituents in a polyfunctional molecule. The lowest numbers possible are given to the substituents (*e.g.* 1-bromo-4-methyl-2-nitrobenzene, **1.56**) and the substituents are listed in alphabetical order.

The reactivity of the positions adjacent to a functional group is often modified by the functional group. Specific names are given to these positions. The position adjacent to an alkene is known as the **allylic** position, whilst that adjacent to a benzene ring is known as the **benzylic** position. In more general cases the Greek letters α, β and γ are used to designate positions adjacent to and progressively further from a functional group. The ω-position is that at the end of a chain. Thus the common amino acids such as alanine (**1.57**) are α-amino acids and but-3-en-2-one (**1.58**) is an α,β-unsaturated ketone. The Greek letters α and β may also have a different stereochemical meaning, but the context usually makes this clear.

When two groups, for example two hydroxyl groups, are adjacent to each other, they are known as **vicinal** groups, whilst two groups attached to the same atom are referred to as **geminal** groups.

An asymmetric centre may be described systematically using the **sequence rules**. The atoms attached to the asymmetric centre are ranked according to their atomic number. The highest number is given the priority 'a' and the lowest 'd'. If, on viewing the carbon–d bond from the side remote from d, the sequence of the three higher atoms around the

1.56

1.57

1.58

asymmetric carbon, a → b → c, is clockwise, the centre is described as *R* (right handed or *rectus*). If the order a → b → c is anticlockwise, the centre is described as *S* (left handed or *sinister*). The full implementation of these rules for the designation of stereochemistry, including that of alkenes, is described in books on stereochemistry.

In a number of cases, particularly with simple molecules, the commonly accepted trivial name is more clearly indicative of their properties, source and reactivity. The IUPAC rules indicate that some of these trivial names are preferred and they are in current common usage in the scientific literature and on the bottles found in the laboratory. However, systematic nomenclature is used for more complex structures, for indexing and for abstracting. Consequently, both have to be known. In this book we will use the common trivial names, giving where appropriate the systematic name as well.

Abbreviations are often used for parts of structures, particularly when these do not participate in a reaction. Thus the symbol R may be used for the remainder of a molecule. The abbreviation Ar may be used for an aromatic ring while Ph is used for phenyl (C_6H_5). Some common abbreviations for alkyl groups are given in Table 1.3.

Table 1.3 Common abbreviations for alkyl groups

Me	methyl	Bu	butyl
Et	ethyl	Bu^t or *t*-Bu	tertiary butyl (*tert*-butyl)
Pr	propyl	Ac	acetyl
Pr^i or iPr	isopropyl	Bz	benzoyl

Another abbreviation used in drawing structures is to draw only the bonds of the carbon framework, leaving out the atoms. Bonds between carbon and hydrogen atoms are also left out. Thus, butane is drawn as a 'zig-zag' and cyclohexane as a hexagon. Double and triple bonds are included as = or ≡. In this book, benzene rings will be drawn as cyclohexatrienes rather than with a circle, because this valence bond representation makes it much easier for the student to understand the mechanism of aromatic substitution. Furthermore, in polycyclic aromatic compounds the use of circles can be misleading.

Electron movement is symbolized by a double-headed 'curly arrow' for the movement of an electron pair, and a single-headed arrow or 'fishhook' for the movement of a single electron. In representing electron movement, the arrow must start from the bond or atom that provides the electron(s) and the arrow should end where the electron movement terminates, either to form a bond or on the particular atom or group that receives the charge. Thus if the electron movement creates a bond,

used for an electron pair

used for a single electron
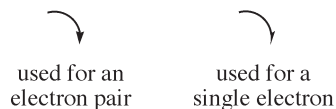
the arrow should terminate where the centre of the new bond will be; if a leaving group departs with the bonding electrons, the arrow should terminate on the atom receiving the charge.

1.2   Reagents and Reactions

1.2.1 Making and Breaking Bonds

The reactions of functional groups involve the making and breaking of bonds. In homolytic reactions the bonding pair of electrons is separated to generate two free radicals, whereas in heterolytic reactions the bonding pair stays with one partner. The reagents that bring about these reactions are thus involved in one- or two-electron processes.

In the laboratory, most reactions take place in solution. What may be considered to be a high-energy process of placing two bonding electrons on to one atom is influenced by the solvent. The solvent can play a major role in the stabilization of the reacting species by associating with the ions which are formed. Thus heterolytic reactions, which produce ionic species, are favoured in dipolar solvents with a high dielectric constant such as water, dimethylformamide (DMF, $HCONMe_2$) or dimethyl sulfoxide (DMSO, Me_2SO), whereas homolytic reactions are favoured by non-polar solvents such as petroleum ether or carbon tetrachloride.

1.2.2 Nucleophiles and Electrophiles

The reagents that bring about heterolytic reactions may be classified as **nucleophiles** and **electrophiles**. Nucleophiles are electron-rich, sometimes anionic, reagents which participate in reactions at centres of electron deficiency in a molecule. A nucleophile forms a bond to the electron-deficient centre by donating both bonding electrons. On the other hand, electrophiles are electron-deficient, sometimes cationic, reagents that react with regions of higher electron density within a molecule. The electrophile forms a bond by accepting both bonding electrons from the other component of the reaction. In Table 1.4, nucleophiles and electrophiles are listed in terms of their position in the Periodic Table.

There are some gaps in terms of common reactive species. For example, although such species or their equivalents can be generated, simple electrophiles based on oxygen (OH^+) and amide nitrogen (NH_2^+) are not commonly used.

1.2.3 Radical Reagents

Free radicals are atomic or molecular entities possessing an unpaired electron. They are formed by homolytic, or one-electron transfer, reac-

	Nucleophiles	Electrophiles
	H^-	H^+ (H_3O^+)
Halogens	F^-, Cl^-, Br^-, I^-	(F^+), Cl^+, Br^+, I^+
Oxygen	H_2O, OH^-, OMe^-, OAc^-	(OH^+)
Sulfur	H_2S, SH^-, SR^-	SO_3H^+
Nitrogen	NH_3, NH_2^-, HNR_2	NO_2^+, NO^+
Carbon	R_3C^-, CN^-, $RC{\equiv}C^-$	R_3C^+, RCO^+

Table 1.4 Nucleophiles and electrophiles

tions. The tendency for an unpaired electron to seek a partner means that, in the absence of special stabilizing features, free radicals are highly reactive species. Nevertheless, it is possible to design situations in which this reactivity can be turned to useful advantage.

Radicals may be generated by thermal means using, as initiators, compounds which possess either a weak O–O bond such as a peroxide, or which, on fragmentation, generate a stabilized radical and a strongly bonded product such as nitrogen gas. Azobisisobutyronitrile (**1.59**) falls into this class. After the loss of the nitrogen, the nitrile stabilizes the adjacent carbon radical by delocalization.
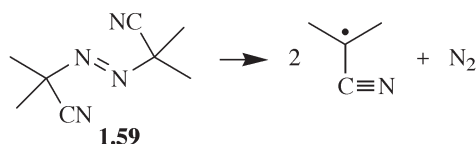
When a molecule is irradiated, particularly with ultraviolet light, some bonds within the molecule can absorb this energy and undergo homolytic cleavage to generate free radicals. These reactions include the formation of alkoxyl (RO•) radicals from alkyl hypoiodites (RO) or nitrites (RONO) or the generation of bromine atoms from bromine or *N*-bromosuccinimide.

A number of radicals may be formed by one-electron transfer redox reactions using a metal ion. These may be either oxidations in which a transition metal ion such as iron(III) accepts a single electron from the organic substrate to become iron(II), or the reaction may be a reduction in which a strongly electropositive metal such as sodium donates an electron to the substrate.

Many radical reactions differ from ionic processes in that they involve a chain of reactions. Once initiated, one radical reacts with another molecule to generate a further radical by breaking another electron pair. This in turn generates a third radical and so on, thus propagating the chain until ultimately it is terminated by the combination of two radicals.
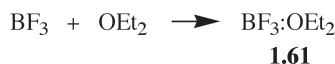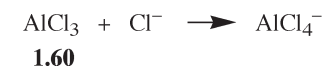
1.2.4 Pericyclic Reactions

There are a number of concerted reactions involving cyclic transition states which are characterized by the maintenance throughout of an overlap between orbitals of the correct symmetry. These reactions are known as pericyclic reactions and the rules that govern them are known as the Woodward–Hoffmann rules. A typical example of a reaction of this type is the Diels–Alder reaction of a diene and a dienophile.

1.2.5 Acids and Bases

The Brønsted theory of acids and bases defines an acid as a proton donor and a base as a proton acceptor, *i.e.* a protic acid such as hydrochloric acid is a source of protons. Although the idea of an acidic hydrogen in organic compounds may initially be understood in terms of a carboxyl hydroxyl group, a hydrogen atom may become weakly acidic in a number of other circumstances, *e.g.* when it is attached to a carbon atom that is adjacent to a carbonyl group. On the other hand, a base such as an amine, or a carboxylate anion, is capable of accepting a proton.

The idea of the proton as the acidic entity was extended by G. N. Lewis. Protons can accept electron pairs from bases; Lewis acids are generalized electron-pair acceptors. For example, aluminium trichloride (**1.60**) behaves as a Lewis acid and reacts with the chloride ion (a Lewis base). Boron trifluoride may react with the lone pair of the oxygen of diethyl ether to form boron trifluoride etherate (**1.61**). A Lewis base is an electron pair donor, in this case the ether oxygen.

$$AlCl_3 \; + \; Cl^- \; \longrightarrow \; AlCl_4^-$$

1.60

$$BF_3 \; + \; OEt_2 \; \longrightarrow \; BF_3{:}OEt_2$$

1.61

The concept of hard and soft acids and bases is useful in classifying reagents. The nature of the outer electron shell of an atom determines its reactivity. If the electron shell is firmly bound and the orbitals are rigidly directed and of low polarizability, then the atom is said to be hard. If the orbitals are less rigidly held and are more polarizable, the atom is said to be softer. Hard acids tend to react with hard bases, and soft acids react with soft bases. Some typical hard and soft acids and bases are given in Table 1.5.
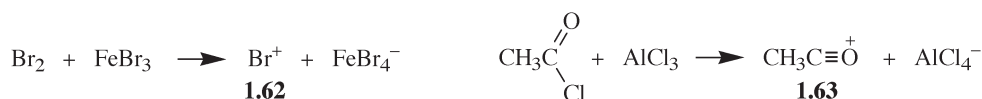
Table 1.5 Hard and soft acids and bases

|	Hard	Borderline	Soft
Acids	H^+, Li^+, Na^+, Mg^{2+}, Ce^{4+}, Ti^{4+}, Cr^{3+}, Fe^{3+}, BF_3, $AlCl_3$, Me_3Si^+	Fe^{2+}, Cu^{2+}	Cu^+, Ag^+, Cd^{2+}, Hg^{2+}
Bases	NH_3, RNH_2, H_2O, OH^-, F^-	C_5H_5N (pyridine), Br^-	H^-, CN^-, R_2S, RS^-, I^-

Acid–Base Catalysis

Many organic reactions are subject to acid or base catalysis. For example, protonation of the oxygen atom of a carbonyl group may enhance the electron deficiency of the carbonyl carbon atom and increase its sensitivity to nucleophilic attack.

The catalyst may serve to generate the reactive species. For example, many electrophiles are generated by mineral acid or Lewis acid catalysts. Bromine reacts with iron(III) bromide to give the bromonium ion (**1.62**), whilst acetyl chloride in the presence of aluminium trichloride reacts as an acylium ion (**1.63**).

$$Br_2 \; + \; FeBr_3 \; \longrightarrow \; Br^+ \; + \; FeBr_4^-$$
1.62

$$CH_3\overset{O}{\underset{Cl}{C}} \; + \; AlCl_3 \; \longrightarrow \; CH_3C\equiv\overset{+}{O} \; + \; AlCl_4^-$$
**1.63**

Base catalysis operates in a similar manner. An acidic proton of a methylene adjacent to a carbonyl group may be removed by a base to generate the reactive nucleophilic carbanion (**1.64**).


1.64
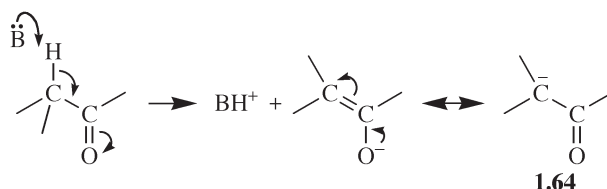
1.2.6 Reaction Types

Having considered the types of bonding, the different functional groups and the types of reagent, it is helpful to divide organic reactions into several large groups. The first group are **substitution reactions** in which one group directly displaces another (Scheme 1.1a). These reactions are typical of σ-bonded C–X systems. **Elimination reactions** (Scheme 1.1b)

(a) Substitution

(b) Elimination
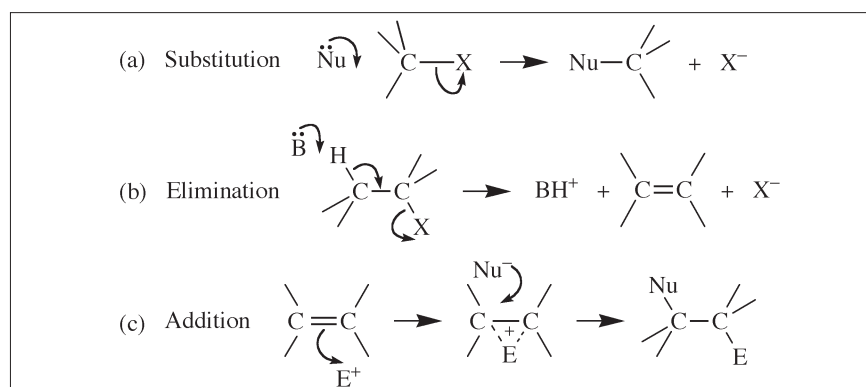
(c) Addition
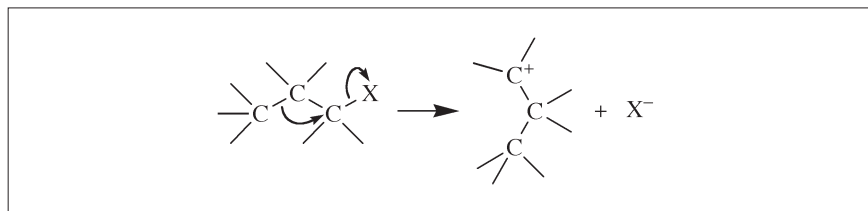
Scheme 1.1

form a second group. Elimination reactions lead to the formation of an unsaturated π-bonded system. The converse of these are **addition reactions**, in which sp or sp^2 centres are converted to sp^2 or sp^3 centres, respectively (Scheme 1.1c). These reactions are typical of π-bonds.

A number of reactions which at first sight appear to be substitution reactions, particularly at sp^2 centres, in fact proceed via an addition–elimination mechanism (*e.g.* Scheme 1.2). Oxidation and reduction reactions may often be regarded as subsets of elimination and addition reactions, respectively. Other oxidation reactions may involve the substitution of a hydrogen atom by an oxygen atom, while some reductions involve the displacement of a substituent by hydrogen (hydrogenolysis). Rearrangement reactions (Scheme 1.3) may be considered as internal substitution reactions.
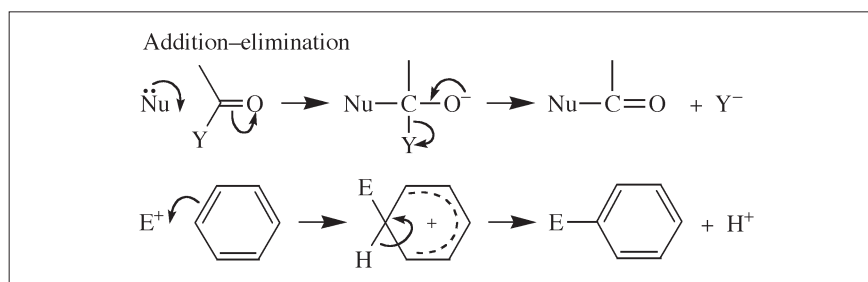

Scheme 1.2

Scheme 1.3

Finally, there is the large family of industrially important polymerization reactions.

1.2.7 The Reaction Coordinate

As a reaction proceeds from starting materials to products, it is possible to show the change of the free energy against the progress of the reaction (the reaction coordinate) and thus identify various stages in the reaction (see Figure 1.1). The activation energy needed to reach the transition state determines the rate of the reaction. In a multi-step process, we can often identify the rate-limiting step.
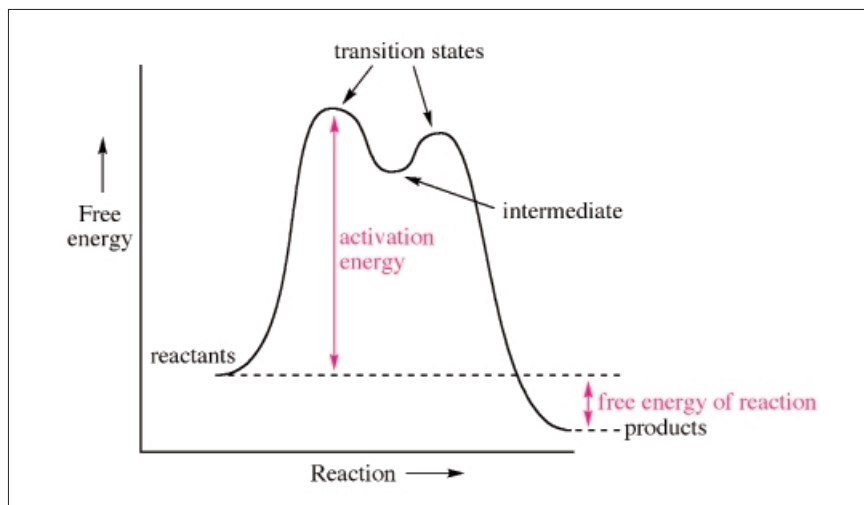
1.2.8 Inductive and Mesomeric Effects

The electronic factors which affect the ground state of a molecule by operating through the σ-bond system, such as the electron-withdrawing effect of a halogen, are known as **inductive effects**. Electronic factors, which operate by the overlap of the p- or π-orbitals of a substituent with the π-orbitals of the rest of the molecule, are known as **mesomeric effects**. The mesomeric effect may modify the reactivity of the ground state of a molecule. Once the reaction is in progress, these effects may stabilize an intermediate by enhancing charge delocalization, leading to the **resonance stabilization** of an intermediate. The resonance stabilization of a carbanion by an adjacent carbonyl group (**1.65**) is an important example of this. A double-ended arrow ($\leftrightarrow$) is used to indicate the existence of these resonance structures.
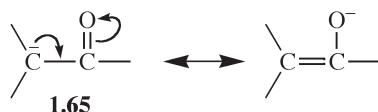
1.2.9 Kinetic *versus* Thermodynamic Control

The features that control the eventual outcome of a reaction may also be illustrated by the reaction coordinate diagram. If there are two possible reaction products with no opportunity to equilibrate between them, the product that has the lowest activation energy (and hence is formed the fastest) will be formed preferentially. The reaction is under **kinetic control**. On the other hand, if the products can equilibrate so that the most stable product is formed (*i.e.* ΔG predominates), the reaction is said to be subject to **thermodynamic control**.

1.2.10 Steric Factors

Hitherto we have considered electronic features which affect the reactivity of a functional group. However, there are a number of general steric factors which need to be considered in terms of the reaction co-ordinate. Although the topic will be dealt with in detail in a companion volume on stereochemistry, some general points need to be made.

The pathway of the incoming reagent approaching an sp^3 centre may strongly influence the chance of a reaction. Obstruction of this pathway by other parts of the molecule will reduce the rate of reaction by **steric hindrance**. Such steric factors can affect the face of a double bond to which groups become attached when a reagent attacks an sp^2 centre. Reagents will attack an alkene or a carbonyl group from the less-hindered face. Hydrogen bonding interactions with a reagent may also favour attack on a particular face. Since an addition leads to the conversion of an sp^2 to a more bulky sp^3 centre, the steric consequences of this have also to be considered.

Many reactions have stereochemically demanding intermediates. The requirements for the optimum overlap of the participating orbitals in many reactions may lead to specific stereochemical relationships between groups in the products of a reaction. Neighbouring functional groups may participate in many reactions, affecting not only the rate but also the products of a reaction. Each of these general stereochemical points needs to be considered for a specific reaction. Functional groups do not exist in isolation, but in real molecules in which the general pattern of reactivity may be modified by their particular environment.

1.3   Learning Organic Functional Group Chemistry

Learning organic chemistry involves rationalizing the reactivity of functional groups in a systematic way so that reactions can be seen to follow a pattern. Recognition of this pattern not only aids the understanding of organic reaction mechanisms, but also reveals those reactions which do not follow the predicted pattern and for which a special explanation must be sought.

A useful method for learning functional group chemistry is to prepare a template, such as the one illustrated in Scheme 1.4. The formula of a typical example of a compound bearing a functional group, for example a ketone such as propanone (acetone), is placed in the centre of a sheet of paper. The template containing three groups of questions is then superimposed on this. The first questions lead to the identification of the sites of electron excess and deficiency in the compound. In the case of propanone, these are the oxygen atom and the carbon atom of the carbonyl group, respectively. Secondly, the types of reaction that the com-

pound undergoes are identified. In the example of propanone, these would be addition reactions. Thirdly, the results of using various reagents for reactions are drawn on to the sheet of paper. For propanone, these would be the products of the addition of various nucleophiles to the carbonyl group. Once a series of reactions have been outlined, it is important to rationalize them in mechanistic terms.
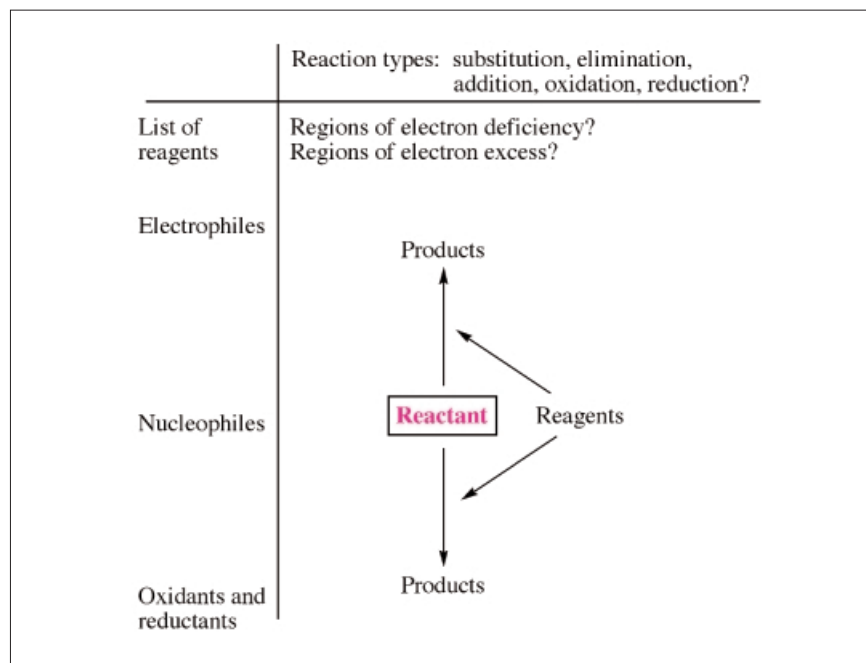
Scheme 1.4 Reaction template

A second strategy is to replace one atom by another close to it in the Periodic Table to reveal analogies and patterns of reactivity. For example, replacing a nitrogen atom by an oxygen atom may reveal analogies between the reactivity of nitriles and carbonyl compounds and between enamines and enols. It may also provide some useful ideas for synthetic methods.

A number of summary charts showing the inter-relationship of functional groups are placed at the end of the sections in Chapters 2, 3 and 4. Students should copy these and place the formulae of appropriate reagents and conditions above the arrows linking the functional groups. The creation of 'spider's webs' linking specific compounds provides a useful method of learning functional group chemistry.

Summary of Key Points

1. The 2s and 2p orbitals of carbon may be hybridized to give the tetrahedral sp^3, planar sp^2 and linear sp arrangements. Carbon may form σ- and π-bonds to other atoms. Two or more π-bonds may be conjugated. A cyclic conjugated system containing $(4n + 2)π$ electrons possesses a particular stability known as aromaticity.

2. Functional groups are inter-related by a series of redox and substitutive transformations. The reactions of functional groups may be determined by the electronegativity differences between the component atoms.

3. Nucleophiles are electron-rich, sometimes anionic, reagents which participate in reactions at centres of electron deficiency in a molecule.

4. Electrophiles are electron-deficient, sometimes cationic, reagents that react with regions of higher electron density within a molecule.

5. Free radicals are atomic or molecular species which possess unpaired electrons.

6. Reactions may be grouped into substitution, elimination, addition, oxidation, reduction and rearrangement reactions.

7. Acids and bases can play an important part in the catalysis of organic reactions.

8. Electronic factors which operate through the σ-bonding system are known as inductive effects whilst those operating through the π-bonding system are mesomeric effects.

9. Resonance effects may stabilize an intermediate.

10. Steric factors may influence both the products and rates of reactions.

Worked Problems

Q Identify the σ- and π-bonds in **1**.
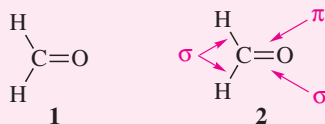
A See **2**. The σ-bonds are derived from the overlap between the sp^2 hybridized orbitals of the carbon and the 1s orbital of the hydrogen atoms and a 2p orbital of the oxygen. These orbitals lie between the atoms. The π-orbital lies above and below the plane of the C=O group and arise from the overlap of the 2p orbitals on the carbon and the oxygen.
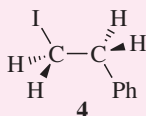
Q Name compound **3**.
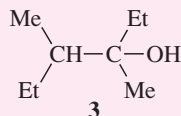
A The longest chain is six carbons and hence the compound is named as a substituted hexane: 3,4-dimethylhexan-3-ol.

Q Draw the preferred conformation of 1-iodo-2-phenylethane.

A See **4**. There is a staggered conformation about the ethane C–C bond with the two bulky groups *trans* to each other.
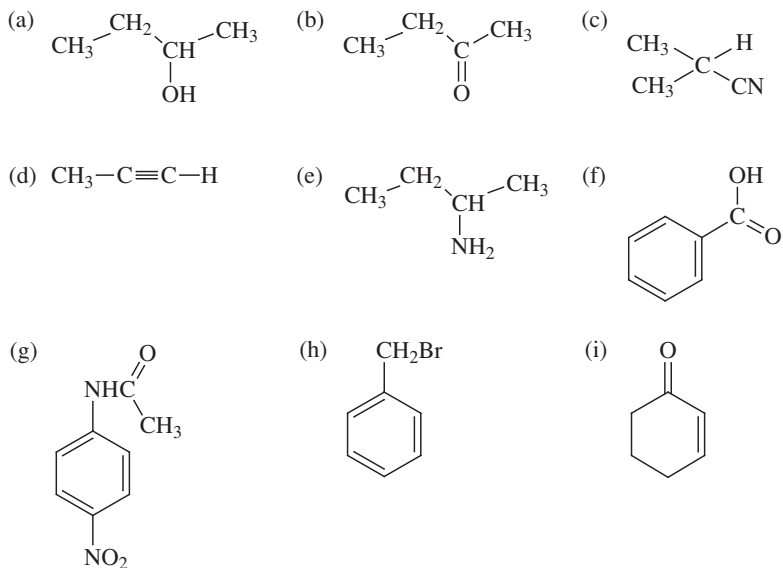

Q From a consideration of the Pauling electronegativity values, predict the charge distribution in the carbon–silicon bond.

A Carbon has a Pauling electronegativity of 2.5 whilst silicon is more electropositive (1.8). Consequently the charge distribution is $C^{\delta-}$–$Si^{\delta+}$.
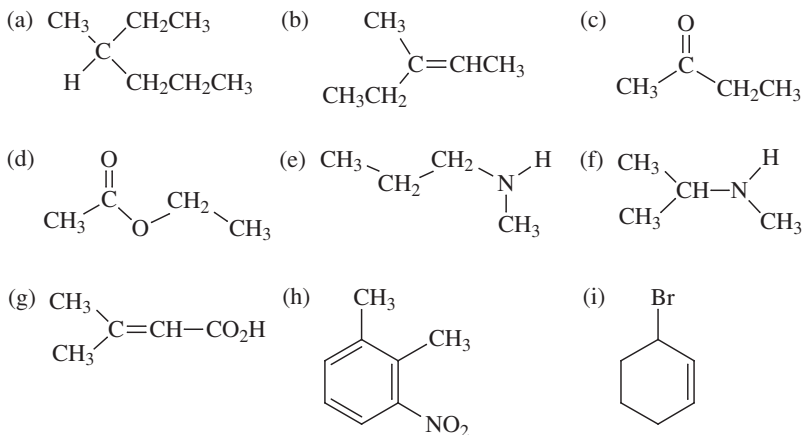
Problems

1.1 (i) Identify the σ- and π-bonds in the following: (a) CH_3CH_2OH; (b) CH_3CHO; (c) $CH_3CH=CH_2$.
(ii) Identify the π-bonds in the following and comment on their structure: (d) $CH_2=CHCHO$; (e) benzene.

1.2 Identify the functional groups in the following structures, and indicate the regions of electron excess (δ+) and electron deficiency (δ−).
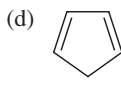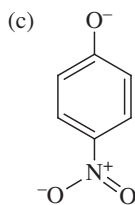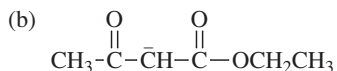
(a)

CH_3—CH_2—CH(—CH_3)—OH

(b)

CH_3—CH_2—C(=O)—CH_3

(c)

CH_3—C(—CH_3)(—H)—CN

(d) CH_3—$C≡C$—H

(e)

CH_3—CH_2—CH(—CH_3)—NH_2

(f)

benzene—C(—OH)=O

(g)

NHC(=O)—CH_3 on benzene ring with NO_2

(h) CH_2Br on benzene ring

(i)

cyclohexenone

1.3 Name the following compounds:

(a) CH_3, CH_2CH_3 / C / H, $CH_2CH_2CH_3$

(b) CH_3 / $C=CHCH_3$ / CH_3CH_2

(c)

CH_3—C(=O)—CH_2CH_3

(d)

CH_3—C(=O)—O—CH_2—CH_3

(e) CH_3—CH_2—CH_2—N(—H)(—CH_3)

(f) CH_3, CH_3 / CH—N(—H)(—CH_3)

(g) CH_3 / $C=CH$—CO_2H / CH_3

(h) CH_3, CH_3 on benzene ring with NO_2

(i) Br on cyclohexene

1.4 Identify the following species as nucleophiles or electrophiles: (a) Br^+; (b) Br^-; (c) CN^-; (d) NO_2^+; (e) NO_2^-; (f) NH_2^-; (g) $RC{\equiv}C^-$; (h) $MeCO^+$.

1.5 Draw resonance structures for the following:

(a) $CH_3{-}CH_2{-}\overset{+}{\underset{H}{C}}{-}OH$

(b) $CH_3{-}\overset{O}{\overset{||}{C}}{-}\overset{-}{C}H{-}\overset{O}{\overset{||}{C}}{-}OCH_2CH_3$

(c)

(d)
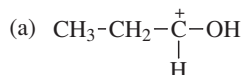
1.6 Draw the three-dimensional structures of the following, indicating the interactions that may exist: (a) *n*-butane in its staggered form; (b) *n*-butane in its eclipsed form about the 2,3-bond; (c) 1,2-dibromoethane in its most stable form; (d) cyclopropane; (e) 1,2-epoxyethane (ethylene oxide) showing the lone pairs of electrons on the oxygen; (f) *cis*- and *trans*-1,4-dimethylcyclohexane in the chair form; (g) *trans*-cyclohexane-1,2-dicarboxylic acid; (h) cyclohexene.